Remarks

Claims 1-32, 34 and 35 are pending in this application. Claim 33 was previously canceled. Claims 1-22 were previously withdrawn in view of Applicants' election. Claim 23 is proposed to be amended. Upon entry of these amendments, claims 1-32, 34 and 35 are pending with claims 23-32, 34 and 35 under active consideration. Claim 23 is amended to correct typographical errors. Support for the amendment to claim 23 may be found in the specification as filed at least at paragraphs [0014] and [0016] (with reference to the published application). No new matter is added by the amendment. Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application.

I. Patentability Arguments

A. Claim Rejections

1) The Rejections Under 35 U.S.C. § 103 Should be Withdrawn

Claims 23-32 and 34-35 stand rejected under 35 USC § 103(a) as being unpatentable over WO 00/08015 (hereinafter, "the '015 publication"), in view Patani *et al.*, Chemical Rev., 96:3147-3176 (1996) (hereinafter "Patani"). Applicants respectfully traverse the rejection based on the amendments proposed herein and on the following arguments.

One of ordinary skill in the art, reading WO00/08015, is not taught the compounds recited in the rejected claims, nor are such compounds suggested. The present invention differs from WO00/08015 by reciting compounds not exemplified therein. This is true despite the fact that WO00/08015 discloses pages upon pages of generic formulas and compounds. The '015 publication discloses over seventeen generic formulae, encompassing, conservatively, hundreds of thousands or millions of compounds. In rejecting the present claims, the Examiner has, with no guidance from the '015 publication, chosen one of these seventeen generic formulas, formula IX, and selected particular substituents from among the list of many different substituents to arrive at "compounds that are very similar to the elected compound." This type of analysis is not sufficient to establish a *prima facie* case of obviousness. "A prima facie case of obviousness for a chemical compound still [post-*KSR*], in general, begins with the reasoned identification of a [prior art] lead compound." *Eisai Co. v. Dr. Reddy's Labs, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Obviousness can then be based on structural similarity along with "some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." Id at 1357. With respect to selection of generic formula IX, the '015 publication lists compounds of general Formulas II through XI-B as "preferred FSH agonists", and lists

compounds of general Formulas XII-XV-B as "especially preferred FSH agonists." With respect to compounds exemplified in the '015 publication, specific chemical compounds are described for general formulas IX, XII, XIII, XIV, and XV. For those specific chemical compounds described for formula IX, *none of the compounds is structurally similar to the presently claimed genus/species*. For example, none of the compounds contain, *inter alia*, a piperazine moiety. Moreover, the working examples of the '015 publication illustrate the synthesis of only six compounds, none of which is structurally similar to those presently claimed: formulas XVI, XVII, XVIII, and XIX (all of which fall under general formula XIII) and formulas XXV, and XXVI (both of which fall under general formulas XIV and XV respectively). FSH activity is demonstrated only for three compounds, none of which are structurally similar to those presently claimed: formulas XVI, XVII, and XIX (all of which fall under general formula XIII). Accordingly, it can be seen that the '015 publication provides no motivation to the skilled person to arrive at a lead compound with structural similarity to the presently claimed species. To the extent guidance is provided by the '015 publication, the skilled person, attempting to identify a lead compound for the production of other compounds having similar utility would look to the three compounds (formulas XVI, XVII, and XIX) for which FSH activity is demonstrated and which fall under general formula XIII, which are described as "particularly preferred FSH agonists" (compare to compounds of general formula IX which are described as "preferred FSH agonists").

Moreover, once a lead compound has been identified in the prior art, in addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-2 (Fed Cir 1985). Specifically, in order to find a *prima facie* case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" is also required.

Id. The '015 publication does not disclose, *inter alia*, compounds having a heteroaryl (e.g. thiophene) or amino group at the R^4 position nor does the '015 publication teach or suggest equivalence between either of these groups at the R^4 position. Indeed, heteroaryl and amino are not listed as a suitable substituents at that position. A person of ordinary skill in the art understands the inherent unpredictability with respect to maintaining the properties of a compound when functional groups are changed. The Examiner characterizes Patani as teaching "that benzene, thiophene, and pyridine rings, in relation to biological activity of pharmaceutical compounds are equivalent bioisosteres of each other…that have similar physical or chemical properties…[and thus] similar biological properties." In fact, the portion of Patani cited by the Examiner only refers to thiophene in passing and provides no examples illustrating equivalence of benzene and thiophene in chemical compounds related or unrelated to those presently claimed. Such does not provide the specific motivation required for a finding of *prima facie* obviousness. One of ordinary skill in the art understands that the use of bioisosteric replacement (classical or nonclassical) in drug design highly dependent on the biological system being investigated. What may be a successful bioisosteric replacement for a given molecule interacting with a particular receptor in one instance, quite often has no effect or abolishes biological activity in another system. No hard and fast rules exist to determine what bioisosteric replacement will work with a given molecule – the medicinal chemist must rely on experience and intuition in order to decide the best approach. Importantly, heteroaryls are conspicuously absent from the list of suitable substituents at the R5 position (corresponding to the R4 position of the present invention) despite being listed as suitable substituents at the R1 and R2 positions. Accordingly, one of ordinary skill in the art would not be motivated to modify the compounds disclosed in the '015 publication by placing a heteroaryl at the R5 position.

In view of the above, Applicants respectfully submit that the '015 publication does not teach or suggest the presently claimed compounds. Absent such a teaching or suggestion, the

presently claimed invention is non-obvious. Accordingly, Applicants respectfully request the Examiner withdraw the obviousness rejection under 35 U.S.C. § 103.

2) The Rejections For Nonstatutory Obviousness-Type Double Patenting Should be Withdrawn

Claims 23-32 and 34-35 stand rejected as being unpatentable over US Patent No. 6,235,755 (hereinafter, "the '755 patent") in view of WO 00/08015 on the ground of nonstatutory obviousness-type double patenting. Applicants respectively traverse the rejection based on the amendments proposed herein and on the following arguments.

Applicants note that the '755 patent is substantially identical to the '015 publication. Thus, for the reasons discussed in detail above, the '755 patent fails to teach or suggest the presently claimed compounds. Absent such a teaching or suggestion, the presently claimed invention is non-obvious. Accordingly, Applicants respectfully request the Examiner withdraw the rejection for nonstatutory obviousness-type double patenting.

CONCLUSION

The Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below with any questions, comments or suggestions relating to this application.

Respectfully submitted,

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